UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/905,592 | 07/13/2001 | Keiya Ozawa | 50026/012003 | 6387 |

21559 7590 05/04/2005

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

| EXAMINER | |
|---|---|
| AKHAVAN, RAMIN | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | |

DATE MAILED: 05/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

05/02/05 RA

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/905,592 | OZAWA ET AL. | |
| | Examiner | Art Unit | |
| | Ramin (Ray) Akhavan | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *5,6,8,10,12,14,15 and 17-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,6,8,10,12,14,15 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *05/04, 02/04, 04/0*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Receipt is acknowledged of a request for continued examination under 37 CFR 1.114, as noted below. Claims 5 and 15 are amended. Claims 5-6, 8, 10, 12, 14-15 and 17-19 are currently pending and under consideration in this action.

All objections or rejections not repeated herein are hereby withdrawn. Where applicable, a response to Applicant's arguments will be set forth immediately following any objection or rejection set forth herein. This action is non-final.

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/28/2005 has been entered.

### *Information Disclosure Statement*

It is believed that all Information Disclosure Statements (IDS) have been sent to Applicants previously or are sent herewith. It should be noted that the IDSs stamped (OIPE date stamp) February 23, 2004 and April 20, 2004 (e.g., Anderson and Gearing et al. respectively as the first listed non-patent publications) are duplicative over the IDSs stamped May 28, 2004 that list the same exact publications. Accordingly, the listings are crossed-through in latter IDSs.

### *Claim Objections*

Claims 5 and 10 are objected to because of the following informalities: The claims recite the term "G-CSF" without setting forth the corresponding definition (i.e., granulocyte colony stimulating factor). Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. **Claims 5-6, 14 and 17-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Base claim 5 recites the term "the G-CSF" which lacks sufficient antecedent support. Furthermore, claim 5 is vague and indefinite because it is unclear whether the deleted region is in the extracellular domain of G-CSF or of G-CSF Receptor (G-CSFR). The specification does not appear to contemplate the former scenario and indeed, the specification teaches that the 5th residue through the 195th residue of the G-CSFR extracellular domain is deleted. (e.g., p. 9, Example 1). However, as written the claim is directed to deletion in the cytokine – G-CSF. Furthermore, the limitation "parts thereof" is vague in that it is unclear whether it is directed to the extracellular portion(s) that is deleted or some other region in the extracellular region.

In addition, claims 14 and 18-19 were rejected previously because the claims recite the term "vector system".

A response to Applicants' arguments is set forth immediately following the rejection that is repeated herein. As stated in the previous action, it is unclear how this term is to be interpreted in determining the claims' metes and bounds, because "system" implies a group of interacting, interrelated or interdependent elements forming a complex whole. The specification does not delimit this embodiment, but rather indicates that a "vector system" *includes* multiple vectors and *comprises*, a vector comprising a fusion protein and a vector comprising an exogenous gene. (e.g. Spec. p. 6, ¶ 2). The term "system", as used in the claims or in the specification, implies additional steps, processes, elements or components, which remain undefined and indefinite. In other words, the specification only indicates that the system can have as one of its elements or components, multiple vectors, but such a teaching does not clarify, what a "system" specifically entails. Thus the specification does not limit the term "vector system" to a degree. In sum, the limitation is open-ended and subjective, thus making indeterminable the claims' metes and bounds.

***Response to Arguments***

Applicant's arguments have been fully considered but they are not persuasive. Applicants assert that in the context of the present invention, "a vector system comprises multiple independent yet interrelated vector molecules, at least one comprising a fusion protein and another comprising an exogenous gene". (Remarks, p. 6, ¶ 2). However, as written there is no indication that the first vector and second vector are interrelated in any temporal or other measure.

Applicants assert and the specification recites "Such a vector system of multiple vector molecules is usually introduced into a cell by co-transformation". (Id., citing the Specification, at

p. 6, last sentence bridging to p. 7). However, that the two vector molecules are co-transformed implies a method step, where no such method step is recited in the claim. In other words, it is unclear whether the claim is directed to a product(s) or to a process. Moreover, it is unclear how the first vector and second vector molecule are interrelated in the claimed "system". For example, is one vector molecule necessary for the other to effect cell proliferation activity? Is proliferation necessary for the first vector molecule "comprising a desired exogenous gene" to express said exogenous gene? It is unclear whether the vectors are required to be present in the same cell (e.g., claim 14; for example, the first vector is in an Eppendorf tube, while the second vector is transformed into a cell, yet as such the vector molecules can comprise a system, where at some later time point the first vector is linearized and used to transduce the host cell).

In sum, given that the claims as written appear to be directed to a product, given that there does not appear to be any level of interrelatedness between the first and second vector molecules, and given that the claims imply a method step, it follows that one of skill is not able to define the claims' boundaries.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Claims 5-6, 8, 10, 12, 14-15 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.**

This rejection was made previously and repeated herein, with modification to clarify the grounds of rejection and to address the amended claim 5. A response to Applicants' arguments is set forth immediately following the body of this rejection.

The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. More particularly, the claims are directed to a genus of nucleic acid structures (i.e., vector molecules) encoding fusion proteins comprising *any* cytokine receptor or *any* proliferation-inducing portions of *any* cytokine receptor fused to *any* ligand-binding domain of *any* steroid hormone, with the functional correlation of selective ligand-induced expansion (i.e., proliferation) of cells via the cytokine receptor portion of the fusion protein.

With respect to claim 5, there is ambiguity as to how the claim is to be interpreted. (See, Rejection No. 1, supra; discussing G-CSF versus G-CSFR). However, in the interest of advancing prosecution, the sequence that is "deleted"[1] is interpreted to be that of the *receptor* extracellular domain (i.e., G-CSFR) and not the G-CSF cytokine. As such, the claim is directed to a genus of nucleic acids that encode an amino acid sequence wherein *any* portion encoding any amino acid residue(s) is deleted. Therefore, the claims are drawn to a vast number of structures each with the correlative function of inducing cell proliferation as a result of ligand-binding domain interaction.

Furthermore, even where the cytokine receptor is delimited to G-CSF (claim 10), the claim is drawn to a genus of structures – "parts thereof" – with the prescribed function of inducing cell proliferation in the context of any ligand-binding domain. Furthter, claim 12 is directed to *any* cytokine receptor.

---

[1] Claim 5 recites in salient part, "[A] portion of the G-CSF extracellular domain has been deleted... ".

The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus. Furthermore, the Guidelines for Written Description state (hereinafter Guidelines):

> "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art" (Federal Register/ Vol. 66, No. 4/Friday, January 5, 2001/Notices, column 1, page 1105). The Guidelines further state, "[t]he claim as a whole, including all limitations found in the preamble, the transitional phrase, and the body of the claim, must be sufficiently supported to satisfy the written description requirement" (at page 1105, center column, third full paragraph). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations. *Lockwood v. American Airlines Inc.* (CA FC) 41 USPQ2d 1961 (at 1966).

The specification does not provide sufficient description for a representative number of structural properties coupled with a known or disclosed structure to function correlation. The specification an example of Ba/F3 or murine mononuclear cells transformed with three variants of one type of cytokine receptor proliferation domain (i.e., murine G-CSF receptor). More particularly, two relevant fusion constructs are disclosed comprising a chimeric G-CSF receptor/estrogen ligand binding domain construct – "GCRER", as well as a construct with portions deleted in the G-CSFR extracellular domain from the 5th to the 195th residue – GCRΔ (5-195)/ER. (e.g., p. 9, Example 1). Therefore, GCRΔ (5-195)/ER and GCRER are the only relevant embodiments that are disclosed.

In sum, two embodiments of a cytokine receptor are disclosed and one embodiment for a hormone ligand-binding domain (HBD), linked to either the wild type G-CSFR or GCRΔ (5-195). No further structures are disclosed where *any* portion of the G-CSFR extracellular domain is deleted in the context of a fusion molecule imparting cell proliferation or where any other HBD is linked to any other cytokine receptor. Further, notwithstanding the boundaries of the extracellular domain for murine G-CSFR, there are hundreds to thousands of potential deletions or combinations of deletions that read on claim 5, where each structure must correlate to the function of imparting proliferation activity. In sum, the lack of disclosure of a sufficient number of embodiments of said fusion proteins results in a description gap in the instant disclosure.

The knowledge in the art does not provide sufficient relevant information to fill the gap present in the instant disclosure. For example, there are a few examples of particular fusion molecules consisting of a cytokine receptor and a hormone ligand-binding domain, whereby the fusion protein imparts cell proliferation. (e.g., *Capon et al.* US 5,837,544; teaching a chimeric constructs encoding a ligand-binding domain or an inducer-responsive clustering domain (ICD) linked to a proliferation signaling domain (PSD); *Nakabeppu et al.* Mol. Cell. Biol. 1993; 13:4157-66; teaching a fusion protein comprising the *FosB* cytokine receptor domain linked to the human estrogen receptor ligand binding domain, whereby *FosB* regulated proliferation of quiescent cells).

However, a handful of examples do not suffice to describe the genus of fusion molecule structures encompassed by the claims, wherein said structures correlate to cell proliferation.

The fusion molecule components (i.e., cytokine receptor domains and hormone ligand binding domains) are the essential element of the invention, but are not shown to be necessarily interchangeable, so that any combination will not necessarily result in the function of imparting cell proliferation. Such fusion constructs are not deemed to be "conventional" in the art, in the context of cell proliferation. (Supra, Guidelines, discussing critical or essential features of a claimed genus and the relative need for description when a feature is conventional in the art).

In sum, given the enormous breadth of the genus of fusion molecules encompassed by the rejected claims, and given the limited description from the instant specification of such fusion molecules, the skilled artisan would not have been able to envision a sufficient number of specific embodiments to describe the broadly claimed genus. Moreover, an applicant claiming a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from other species (i.e., different combinations of receptors/binding domains comprising a given fusion molecule). Therefore, the skilled artisan would reasonably have concluded that applicants were not in possession of the claimed invention.

***Response to Arguments***

Applicant's arguments have been fully considered but they are not persuasive. Applicants assert several arguments, which are summarized as follows: (1) DNA structural features are common to all members of the genus; (2) distinguishing characteristics for the claimed fusion proteins are sufficiently disclosed; (3) cytokines proliferation-inducing domains or parts thereof are well studied and substantially similar with little variation across species, thereby a limited number of embodiments constitutes possession of the claimed genus;

and (4) a mere review of the literature is sufficient to distinguish cytokine receptors that are predictably operable as fusion proteins.

First, the DNA structural features of either cytokine receptors or hormone ligand-binding domains (HBD) are not common to the members of the genus of claimed fusion molecules. Each protein is encoded by a distinct DNA structure. Furthermore, even for G-CSFR there is considerable variability across species. (e.g., Fukunaga et al. PNAS, 1990; 87:8702-06; teaching that human and mouse G-CSF receptor cDNA comprised 62.5% homology). Otherwise, if DNA structures were interchangeable in structure/function (e.g., cDNA encoding a particular receptor domain), then any cytokine receptor linked to a ligand-binding domain would be obvious over any other cytokine receptor, wherein the receptors are linked to a HBD (e.g., the cytokine receptor of Janus kinases, which is in the same family of receptors as G-CSF). While cytokine receptor families may share certain structural organization (e.g., particular sequence motifs), such organization does not necessarily translate to a shared DNA structure and function.

Second, the distinguishing characteristics for the claimed fusion proteins are not sufficiently described in the instant disclosure nor are such fusion structures provided for by knowledge in the art. Cytokine receptors do share some structural organization of particular motifs, but such does not necessarily translate to interchangeability in the context of fusion proteins. For example, based on distinct structural organization, cytokines are classified in distinct groups (e.g., Ibelgaufts, H. *Cytokine Receptor Families*, pages 1-4, available at <copewithcytokines.de/cope.cgi?002595> (last accessed 04/27/05)). Therefore, not all cytokine receptors are structurally interchangeable.

Furthermore, if the receptors are not interchangeable then it follows that there would be unpredictability with respect to any cytokine receptor being linked to any HBD. For example, G-CSFR is not necessarily interchangeable with IL10 given that the receptors are encoded by entirely different sequences and differ with respect to their organizational structure as well (e.g., modules comprising the extracellular or signal-transducing domain).

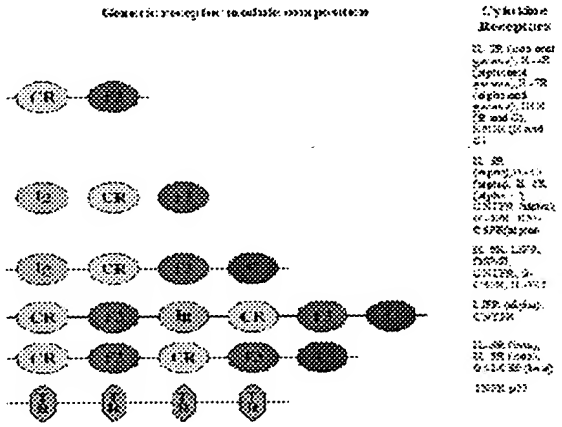
With respect to deletions anywhere within the G-CSFR extracellular domain, deletions would affect the very sequence motifs upon which receptor families are classified (e.g., conserved Trp-Ser-X-Trp-Ser or WSXWS extracellular motif in Type-1 family). Therefore, one cannot rely upon such shared structural organization, where the extracellular domain is deleted, including regions of shared organizational structure (e.g., as between G-CSFR and IL6). In other words, one cannot assert the shared organizational structure as support for filling the description gap, where sequence(s) in the very region comprising shared structural motifs are deleted.

Third, while there is information available with respect to cytokine receptor domains, including the intracellular, transmembrane and extracellular domains, the information available is not necessarily relevant to operation of said domains as a fusion molecule with any HBD. For example, while certain sequence motifs are conserved amongst a group or family of cytokine receptors, each block of conserved sequence is separated by variable linker regions, wherein a single residue can affect folding, which in turn will affect secondary and tertiary structure, which will further affect functionality in relation to a fusion protein. (e.g., Bazan, J.F. Proc. Natl. Acad. Sci. 1990; 87:6934-38, page, 6936, Figure 1; depicting sequence/structure alignment for several cytokine receptors). Therefore, describing a limited number of embodiments (G-CSFR and GCRΔ (5-195)/ER) does not constitute possession of the vast genus of fusion proteins.

Moreover, the cytokine receptor families and subfamilies are grouped based in significant part on the ligand-binding similarities. (Id., pp. 1-2). Thus, the perceived structural/functional similarities based on said binding properties do not present relevant information in regard to structural/functional correlation in the context of fusion molecules, because said fusion molecules comprise a *heterologous* ligand-binding domain (i.e., HBD) linked to said cytokine receptor, or a G-CSF deletion mutant (e.g., GCRΔ (5-195)/ER). Put another way, the similarities observed for a given family of cytokine receptors do not necessarily equate to the cytokine receptors functioning interchangeably when linked to any HBD. For example, based on a given combination of a receptor linked to a HBD (e.g., wild type receptor and HBD), the two resulting ligand-binding domains may be subject to steric hindrance as between each other, in the context of the fusion molecule functioning to impart cell proliferation. Furthermore, with respect to deletions in any portion of the G-CSFR, even deletion of a single residue may render the molecule unstable. (e.g., Fukunaga et al. Embo J. 1991; 10:2855-65, p. 2863, col. 1, ¶ 1).

With respect to Applicants' last assertion, a review of the literature is not sufficient to distinguish cytokine receptors with respect to predictable or interchangeable functionality in relation to fusion proteins. The literature teaches that there are distinguishable sequence and structural characteristics amongst the various cytokine receptors families. Notably, "each cytokine also exhibits some specific activities ...[whereby]... the ability of a cell to respond to each of these [cytokine factor] factors specifically appears to be regulated by the specific expression of distinct receptor chains". (Taga et al. FASEB J. 1993; 7:3387-96; p. 3391, last ¶ bridging to p. 3392).

Therefore, it is unclear how such variance can be translated into interchangeability for *any* cytokine receptor linked to *any* HBD to impart proliferation of any cell. The prior art merely teaches that cytokine receptors within certain families, which comprise some shared combination of conserved sequence motifs, function similarly to bind their cognate cytokines. However, the issue is not whether the structural organizational similarities are predictive for a given cytokine receptor to function to bind a cognate cytokine in a cell, but whether a fusion protein will function predictably where any receptor and any HBD comprise the fusion protein. In fact, there is a great deal of variability with respect to the modules or domains present in a given cytokine receptor and indeed, cytokine receptors are grouped based on the presence of distinct modules:



(See, Cytokines Web, Cytokine Receptor Classification according to domain composition, pp. 1-2, available at <www.cmbi.bjmu.edu.cn/cmbidata/cgf/CGF_Database/cytweb/ Recap_class>, last accessed 04/27/05; teaching at least six different combinations of modules present in certain cytokine receptors' extracellular portions; G-CSFR is depicted in the third group from the top).

Therefore at least to the extent that different receptors are comprised of a distinct set or distinct combination of modules, it is reasonable to expect unpredictability as to any fusion molecule functioning to impart proliferation. In addition, there are a significant number of cytokines and cytokine receptors for which there is relatively little information available (e.g., glial growth factor and GCP-1 to name a couple; *see also*, Ibelgaufts, H., supra, for a more extensive list).

With respect to the proliferative or signal-transducing domains, the literature clearly sets forth several distinct structures, used to group certain families of cytokine receptors. (supra, Taga et al. 1993, page 3388, Figure 1; illustrating the multiple different cytoplasmic regions of various cytokine receptors). Therefore, the signal-transducing or proliferative domains are structurally distinct, especially where the receptors are from different families or subfamilies. Moreover, it is unclear whether the signal-transducing domain is exclusively limited to the cytoplasmic module of any particular cytokine receptor.

In sum, for the reasons stated in the foregoing, it must be deemed that a sufficient number of nucleic acid structures encoding the fusion proteins of the invention have not been disclosed, nor is such a lack of disclosure provided for in the prior art.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

3. **Claims 8, 12, 14, 15, 17 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakabeppu et al. (Mol. Cell. Biol. 1993; 13:4157-66; see whole document).**

The claims are directed to a vector encoding a fusion protein comprising a cytokine receptor domain linked to a hormone ligand-binding domain (HBD) and comprising an exogenous gene. The limitation "exogenous gene" is interpreted as broadly as reasonable in light of the full disclosure to read on virtually any gene (i.e., not particularly limited, Specification, p. 7, second full paragraph). In addition, the limitation "vector system" is interpreted as broadly as reasonable to read on any occurrence or teaching where a vector encoding said fusion protein and a vector comprising an exogenous gene are present, without any particular limitation as to interrelationship between the two vectors (claims 14). Furthermore, an isolated cell carrying the "vector system" reads on a cell carrying the vectors

without any particular temporal limitation. In addition, the limitation "kit" is interpreted to mean any container or compartment containing the vector of claim 8.

Nakabeppu et al. teach proliferative activation in cells wherein proliferation is induced by cell transfection with a vector encoding a fusion protein where the estrogen HBD is linked to the cytokine *FosB*. (e.g., Abstract; p. 4157, col. 2, bridging to p. 4158; p. 4159, Figure 2). *FosB* intrinsically comprises dimerization domains. (e.g., Dobrzanski et al. Mol. Cell. Biol. 1991; 11:5470-78; e.g., Abstract; this reference is merely cited to show the intrinsic property for the cytokine *FosB*).

In addition, the vector comprises an exogenous gene (i.e., hygromycin). (e.g., p. 4157, col. 2, ¶ 2). Isolated cells are transfected with said vectors. (e.g., p. 4157, under "Cell culture"; p. 4158, col. 2, ¶ 4). Furthermore, cell culture containers read on a container comprising said vectors (i.e., kit). Furthermore, the reference teaches multiple vectors comprising a "system" where proliferative activation is studied in cells, wherein one vector encodes the fusion protein and another vector encodes an exogenous gene – methyltransferase (MGMT). (e.g., p. 4158, col. 2, under "Results"). In sum, the reference anticipates the rejected claims.

4. **Claims 5-6, 8, 10, 12, 14, 15, 17 and 19 rejected under 35 U.S.C. 102(e) as being anticipated by Capon et al. (US 5,838,544; reference of record; hereinafter the '544 patent).**

A response to Applicants' arguments is set forth immediately following the body of this rejection which was made previously and is repeated herein. The rejection is modified insofar as it is now applied to claims 14 and 1, and to point out the reference's relevant teachings in light of

amendment to claim 5. Claim 5 reads on deletion of any sequence(s) of the G-CSF receptor extracellular domain, notwithstanding the ambiguity noted above. (supra, Rejection No. 1)

Additional claims are interpreted consonant with the interpretations stated above.

The '544 patent teaches a chimeric constructs encoding a ligand-binding domain and a proliferation signaling domain (PSD), as well as vectors and cells containing said constructs. (e.g. Abstract; columns 22-25, Example 1; describing construction of various fusion proteins). The chimeric constructs also encode transmembrane domains (i.e., exogenous genes). (e.g., col. Figure 1). Alternatively, the nucleic acid constructs encoding the fusion proteins are mobilized into pBLUESCRIPT® vector backbone which comprises antibiotic selective genes exogenous gene) for maintenance and selection of the plasmids (e.g., in bacterial propagation). (e.g., col. 23, l. 22).

In addition, the chimeric construct can comprise an inducer-responsive clustering domain (ICD), i.e. hormone receptor domain, which upon binding the inducer or ligand will dimerize or cluster. (e.g. col. 3, ll. 33-39; See also, Fig. 1). Furthermore, the ICD domains can be eukaryotic steroid receptor molecules, including estrogen, progesterone, androgen, for example. (e.g. col. 14, last ¶). In addition, the PSD portion of the chimeric construct can be the transducing domains (i.e. proliferation domains) of the cytokine receptors, including IL-2 for example. (e.g. col. 16, last ¶ bridging to col. 17, ll. 1-19). Further, the PSD can be G-CSF. (e.g. col. 9, l. 54).

With respect to the limitation "vector system", the reference teaches multiple vectors (cols. 22-36, Examples 1-8). Furthermore, human 293 cells are transfected with various vector constructs. (e.g., col. 39, Example 10). Since, there is no temporal limitation as to the vectors

being contained in a cell, then multiple vectors of a "system" of vectors can be present in a cell at different times (i.e., different trasnfection events of 293 cells).[2]

In addition, with respect to deletions of the G-CSFR, the reference teaches that certain amino acid sequences, of the gene(s) comprising the fusion protein, may in some instances be deleted, usually not more than 20 or 30 amino acids. (e.g., col. 14, ll. 11-27). More particularly the deletions can occur at the ends of the gene (e.g., N- or C-terminus of the extracellular domain). (e.g., col. 14, l. 11). Therefore, the reference anticipates the rejected claims.

***Response to Arguments***

Applicant's arguments have been fully considered but they are not persuasive. Applicants assert that the '544 patent does not teach deletion of any portion of the G-CSF extracellular domain. (Remarks, p. 14). It is presumed that when Applicants recite "G-CSF", they mean to refer to the G-CSF receptor (G-CSFR). As noted above, the '544 patent teaches that upto around 30 amino acids may be deleted on the receptor protein domain. (col. 13, last ¶, bridging to col. 14, ll. 1-25). Therefore, the rejection is maintained.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ormum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

[2] The specification indicates that usually vectors are co-transformed, but this limitation is not claimed.

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. **Claims 5, 6, 8, 10, 12, 14, 15 and 17-19 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6-8, 10-14, 16-18 and 20 of copending Application No. 10/100,471.**

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. This rejection was set forth previously and repeated herein. Applicants have not presented any arguments in regard to this rejection but merely assert that this rejection will be addressed at a later time, pending resolution of other rejections. (Remarks, p. 14).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are directed to biologically and patentably indistinguishable subject matter. But for some alterations in the language of the claims, the subject matter is similar in each set of claims. For example, instant base claim 1 is directed to a vector comprising a gene encoding a fusion protein, while reference base claim 1 is directed to a fusion protein comprising the same limitations of having a ligand-binding domain from a steroid receptor and a cytokine receptor domain or part thereof that imparts proliferation activity.

Furthermore, reference claims 6 and 7 are further directed to vectors DNA and vectors comprising the DNA that encodes the fusion protein of reference claim 1. Thus, but for semantic changes and the order of terms such as "vector" and "fusion protein" the claims are directed to patentably indistinguishable subject matter. Additional claims are directed to cells (instant

claims 6, 15, 19: reference claims 8), kits containing said DNA constructs (instant claim 17; reference claim 20) as well as additional vectors encoding an exogenous gene (instant claims 14, 18, 19: reference claims 10-14). Therefore, the instant and reference claims are necessarily obvious over one another.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

GERRY LEFFERS
PRIMARY EXAMINER